



METHOD FOR TREATING MULTI-DRUG RESISTANT TUMORS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/467,070, filed April 30, 2003 and is a continuation-in-part of U.S. application serial no. 10/057,839, filed January 25, 2002, now pending, which is a continuation of U.S. application serial no. 09/556,610, now U.S. Patent No. 6,365,179, which claims the benefit of U.S. Provisional Application No. 60/130,897, filed April 23, 1999. Each of these priority documents are incorporated herein by reference in their entirety.

Field of the Invention

[0002] The present invention relates to a method for reducing the cytotoxicity of mitomycin C, and to a method of administering mitomycin C to a multi-drug resistant cell. Mitomycin C is provided in the form of a prodrug conjugate comprised of a hydrophobic moiety linked to the drug via a cleavable linkage. More particularly, the prodrug conjugate is comprised of a lipid linked to the drug via a cleavable linkage, the lipid being incorporated into a liposomal formulation. The prodrug conjugate is cleavable under mild thiolytic conditions *in vivo* for release of mitomycin C in an unmodified state.

Background of the Invention

[0003] Mitomycin is an established chemotherapeutic agent given for several different types of cancer, including breast, stomach, gullet and bladder cancer. The agent acts by cross-linking DNA so the cancer cells are unable to proliferate. When given intravenously to patients, common side effects due to the toxicity include fever, nausea, vomiting, bone marrow depression, and others (HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, Wilson *et al.*, Eds., 12th Editions, Part Eleven, page 1592, 1991). Drug toxicity is not the only problem associated with chemotherapy. Another problem is drug resistance. Some tumor types, *e.g.*, non-small cell lung cancer and colon cancer, exhibit primary resistance, *i.e.*, absence of response on the first exposure to currently available, conventional chemotherapeutic agents. Other tumor types exhibit acquired resistance, which develops in a number of drug-sensitive tumor types. Drug resistant cancer cells demonstrate two types of acquired drug resistance; cells exhibiting single agent resistance or resistance to single class of anti-cancer drugs with the same mechanism of action. The second type involves cells broadly resistant to several or